b) determining whether said polypeptide binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

REMARKS

Claims 1-3, 11-12, 15-21, 23 and 24 were pending in the application. Claims 20, 21 and 23 have been cancelled, without prejudice, claims 17, 19 and 24 have been amended and new claim 25 has been added. Accordingly, after the amendments presented herein have been entered, claims 1-3, 11-12, 15-19, 24 and 25 will remain pending. For the Examiner's convenience all of the pending claims are set forth in Appendix A.

Support for the amendments to the specification can be found at page 1, lines 6-11 where the entire contents of U.S. Patent Application No.: 09/298,731 were incorporated by reference into the instant application. The paragraphs that have been inserted into the instant specification begin at page 32, line 35 of the '731 application. Applicants respectfully submit that as required by 37 C.F.R. 1.75 (d)(1) and MPEP § 608.01 (o), the present specification has been amended to recite the specific sections from the '731 patent application which provide support for the amendments to the claims.

Support for the amedments to the claims and for new claim 25 can be found throughout the specification including the originally filed claims. Specifically, support for the amendments to claims 17 and 19 can be found, for example, in Figure 41 and Example 10. Support for new claim 25 can be found in claim 1 as originally filed and in the section inserted into the specification by the amendment presented herein.

Attached hereto is a marked-up version of the changes made to the claims and the specification by the current amendments. The attached page is captioned "**Version With Markings to Show Changes Made.**"

No new matter has been added. Any amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to

expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Allowed Claims

Applicants gratefully acknowledge the Examiner's indication of claims 1 and 2 as allowed (see Office Action Summary accompanying the present Office Action).

Acknowledgement of the Examiner's Withdrawal of Certain Rejections

Applicants gratefully acknowledge the Examiner's withdrawal of: (a) the previous rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph; (b) the previous rejection of claims 1-3, 11-12, and 15-16 under 35 U.S.C. § 102; and (c) the previous rejection of claims 1-3, 11-12 and 15-23 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-3, 11-12, 15-16 and 17-23 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-3, 11-12, 15-16 and 17-23 under 35 U.S.C. § 112, first paragraph because, according to the Examiner, " ***the specification, while being enabling for a method of identifying a compound suitable for treatment wherein the PCIP is 9q***, does not provide enablement for a method of identifying a compound suitable for treatment wherein the polypeptide is a fragment of PCIP 9q." (***Emphasis added***). Specifically, the Examiner is of the opinion that

> Applicant has added the limitation "biologically active" to attempt to better define the function of the fragments of PCIP 9q. There is insufficient guidance as to the nature of the fragments which Applicants claim. There is insufficient guidance provided in the specification as to the relationship between the structure of PCIP 9q and its function.

To begin with, Applicants respectfully submit that claims 1-3 are not directed to methods which use fragments of PCIP polypeptides. Rather, these claims are directed to methods which use the full length PCIP polypeptides of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28. Thus, this rejection does not apply to claims 1-3 and, in fact, the Examiner has already indicated claims 1-2 as allowed (see the Office Action Summary accompanying the present Office Action).

With respect to the remaining "fragment" claims, Applicants respectfully traverse the foregoing rejection for the reasons of record. However in the interest of expediting prosecution, Applicants have amended claims 17 and 19 to recite ***specific*** fragments of the 9q polypeptides that have been shown to be biologically active in Applicants' specification. For example, Applicants' specification discloses at page 53, lines 11-14, as well as in Figure 21, that the 9q polypeptides of the invention contain calcium binding domains (EF hands) that are important for the activity of the 9q molecules. In Example 10, Applicants also report that mutations in the three EF hands of PCIPs completely eliminate the effects of PCIPs on Kv4 channel kinetics and conclude that the interaction of PCIPs with Kv4 channels is calcium dependent. As a result, a fragment of a 9q polypeptide comprising a calcium binding domain (an EF hand) is biologically active and could be used in the claimed methods without any undue experimentation.

In Example 10, Applicants also disclose the generation of N-terminal deletions of the 9q polypeptide. Applicants have demonstrated that deletion of the N-terminal residues (amino acids 2-67) of the human 9q protein did not alter the function of the 9q molecule, *e.g.*, the ability of the molecule to modulate Kv4.2 current amplitude and kinetics (page 49, line 33 through page 50, line 2 of the specification). Thus, Applicants have demonstrated that the 67 N-terminal amino acid residues of the 9q polypeptide are not critical for the function of this molecule. As a result, a fragment of a 9q polypeptide comprising amino acid residues 68-252 is biologically active and could be used in the claimed methods without any undue experimentation.

In view of the foregoing, Applicants respectfully submit that an ordinarily skilled artisan following the teachings in Applicants' specification would have been able to practice the claimed invention using only routine experimentation. Accordingly, the aforementioned rejection of the pending claims under section 112, first paragraph, is improper, and Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

With respect to the new claim 25 directed to methods which use polypeptides that are at least 95% identical to SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28 and retain a PCIP activity, Applicants would like to bring to the Examiner's attention Example 14 of the *Revised Interim Written Description Guidelines Training Materials*. This example provides that a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single

species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rationale behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity." The Guidelines also provide that "***[t]he procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.***"

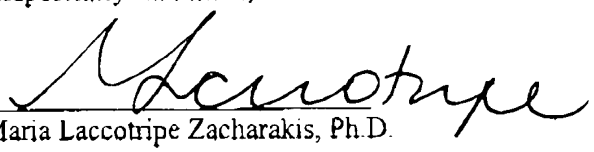
Similarly, in the present case, claim 25 is directed to methods which use polypeptides comprising an amino acid sequence that is at least 95% identical to the amino acid sequence shown in SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, wherein the polypeptide retains a 9q PCIP activity. As set forth in Example 14 of the Written Description Guidelines, the production of polypeptides which contain a 5% variation from a specific sequence is routine in the art. Furthermore, Applicants have disclosed in the instant specification assays for identifying all of the at least 95% identical variants of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28 that retain a 9q PCIP activity (see, for example, page 50, line 34 through page 55, line 13 of the specification).

In view of the above, Applicants respectfully submit that an ordinarily skilled artisan reading the foregoing teachings in Applicants' specification would have been able to practice the claimed invention using only routine experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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Limited Recognition under 37 C.F.R. § 10.9(b)

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Dated: February 19, 2003

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 13, line 26, please insert the following:

--In a preferred embodiment, the PCIP protein has an amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, or SEQ ID NO:40. In other embodiments, the PCIP protein is substantially homologous to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, or SEQ ID NO:40, and retains the functional activity of the protein of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, or SEQ ID NO:40, yet differs in amino acid sequence due to natural allelic variation or mutagenesis. Accordingly, in another embodiment, the PCIP protein is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, or SEQ ID NO:40.

In the claims:

17 **(Amended)** A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a biologically active fragment of a 9q PCIP polypeptide ~~comprising at least 10 amino acid residues of a~~ comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, wherein said biologically active fragment is selected from the group consisting of an EF domain, residues 68-252 of human 9q, and a Kv4.3 or Kv4.2 potassium

channel α subunit binding domain, or a cell expressing said biologically active fragment of said 9q PCIP polypeptide with a test compound; and

b) determining whether said biologically active fragment binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

19. **(Amended)** A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a biologically active fragment of a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, ~~comprising at least 10 amino acid residues of a~~ wherein said biologically active fragment is selected from the group consisting of an EF domain, residues 68-252 of human 9q, and a Kv4.3 or Kv4.2 potassium channel α subunit binding domain, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said biologically active fragment of said 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder.

24. **(Amended)** The method of claim ~~20~~ 17 or 19, wherein the EF domain is selected from the group consisting of:

a) residues 116-127, 153-164, 189-200, or 237-248 of SEQ ID NO:14;

b) residues 103-114, 140-151, 176-187, or 224-235 of SEQ ID NO:16;

c) residues 116-127, 153-164, 189-200, or 237-248 of SEQ ID NO:18;

d) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:20;

e) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:22;

f) residues 116-127, 103-114, 139-150, or 187-198 of SEQ ID NO:24;

g) residues 66-77, 103-114, 189-200 or 237-248 of SEQ ID NO:26; and

h) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:28.

Appendix A

1. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, or a cell expressing said 9q PCIP polypeptide with a test compound; and

b) determining whether said 9q PCIP polypeptide binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

2. The method of claim 1, wherein the binding of said test compound to said 9q PCIP polypeptide, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/polypeptide binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

3. A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder.

11. The method of any one of claims 1, 3, 17 or 19 wherein said cardiovascular disorder is associated with an abnormal I_{to} current.

12. The method of any one of claims 1, 3, 17 or 19, wherein said 9q PCIP is a human 9q.

15. The method of any one of claims 1, 3, 17 or 19, wherein said cardiovascular disorder is long-QT syndrome.

16. The method of any one of claims 1, 3, 17 or 19, wherein said cardiovascular disorder is congestive heart failure.

17. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a biologically active fragment of a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, wherein said biologically active fragment is selected from the group consisting of an EF domain, residues 68-252 of human 9q, and a Kv4.3 or Kv4.2 potassium channel α subunit binding domain, or a cell expressing said biologically active fragment of said 9q PCIP polypeptide with a test compound; and

b) determining whether said biologically active fragment binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

18. The method of claim 17, wherein the binding of said test compound to said biologically active fragment of said 9q PCIP polypeptide, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/biologically active fragment binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

19. A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a biologically active fragment of a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, wherein said biologically active fragment is selected from the group consisting of an EF domain, residues 68-252 of human 9q, and a Kv4.3 or Kv4.2 potassium channel α subunit binding domain, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said biologically active fragment of said 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder.

24. The method of claim 17 or 19, wherein the EF domain is selected from the group consisting of:

a) residues 116-127, 153-164, 189-200, or 237-248 of SEQ ID NO:14;

b) residues 103-114, 140-151, 176-187, or 224-235 of SEQ ID NO:16;

c) residues 116-127, 153-164, 189-200, or 237-248 of SEQ ID NO:18;

d) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:20;

e) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:22;

f) residues 116-127, 103-114, 139-150, or 187-198 of SEQ ID NO:24;

g) residues 66-77, 103-114, 189-200 or 237-248 of SEQ ID NO:26; and

h) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:28.

25. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a polypeptide that is at least 95% identical to a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28 and retains a 9q PCIP activity, or a cell expressing said polypeptide with a test compound; and

b) determining whether said polypeptide binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.